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Studies on Nitrogen-containing Heterocyclic Compounds. XXXIV.[1] Chemical Reactivity of 1(or 2)-Cyano-1,2-dihydro(iso)-quinolines and 1(or 2)-Cyano-1,2,3,4-tetra-hydro(iso)quinolines

Yoshiki Hamada and Michiharu Sugiura

Faculty of Pharmacy, Meijo University[2]

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Chemical reactivity of quinoline and isoquinoline skeletons was compared, using 1-cyano-2-methoxy-1,2-dihydroquinoline (**2a**), 2-cyano-1-methoxy-1,2-dihydroisoquinoline (**2b**), 3-bromo-1-cyano-2,4-dimethoxy-1,2,3,4-tetrahydroquinoline (**3a**), and 4-bromo-2-cyano-1,3-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**3b**), in order to know the fundamental chemical characteristics of **2a**, **b** and **3a**, **b** for use as an intermediate for the syntheses of nitrogen-containing heterocyclic compounds.

1) Oxidation of **2a** or **2b** and **3b** afforded 2-one compound or 1-one compounds.

2) Reaction of **2a** or **2b** with ethanethiol afforded 1(or 2)-cyano-2(or 1)-ethylthio-1,2-dihydroquinoline (**2e**) or -1,2-dihydroisoquinoline (**2f**). Reaction of **3a** with ethanethiol gave 4-bromo-2-cyano-1-ethylthio-3-methoxy-1,2,3,4-tetrahydroisoquinoline (**3i**) but **3b** did not react with this reagent.

3) Bromination of **2e** and **2f** in methanol respectively gave **3a** and **3b**.

4) Reaction of 2-cyano-3,4-dibromo-1-methoxy-1,2,3,4-tetrahydroisoquinoline (**3c**) with ethanethiol or diethylamine afforded 3-bromo-2-cyano-1,4-diethylthio-1,2,3,4-tetrahydroisoquinoline (**3d**) or 4-bromo-2-cyano-3-diethylamino-1-methoxy-1,2,3,4-tetrahydroisoquinoline (**3g**).

5) Alkaline hydrolysis of **3d** and **3i** produced 1-ethylthioisoquinoline. Acid hydrolysis of **3b**, **d**, **g**, **i** resulted in the formation of isoquinolines with the 4-substituent intact.

6) Alkaline hydrolysis of **3b** or **3d** in alcohol afforded N-iminoethers, while similar reaction in hydrogen peroxide N-carboxamides.

Keywords——tetrahydro(iso)quinoline; von Braun reaction; hydrolysis; oxidation; dihydro(iso)quinoline; thio(iso)quinoline; addition; bromination

We have already reported the synthesis of 3-bromoquinolines and 3-alkoxyisoquinolines from quinoline (**1a**) and isoquinoline (**1b**) *via* 1(or 2)-cyano-1,2-dihydroquinoline (**2a**) or -iso-

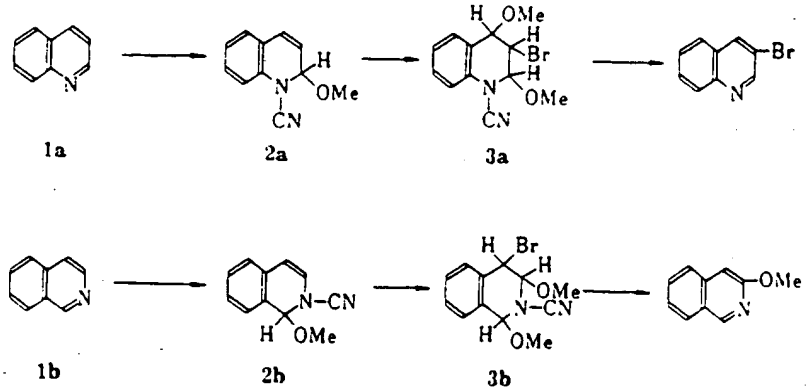


Chart 1

1) Part XXXIII: Y. Hamada, M. Sugiura, and M. Hirota, *Yakugaku Zasshi*, **98**, 1361 (1978).
2) Location: *Yagoto-Urayama, Tempaku-ku, Nagoya 468, Japan.*

quinoline (**2b**) and/or 1(or 2)-cyano-1,2,3,4-tetrahydroquinoline (**3a**) or -isoquinoline (**3b**)[1,3] (*cf.* Chart 1). It seems important to know the fundamental characteristics of **2a**,**b** and **3a**,**b** in order to synthesize nitrogen-containing heterocyclic compounds using **2a**,**b**, **3a**,**b**, and their related compounds. Therefore, comparative examinations were made on the chemical nature of **2a** and **2b**, and of **3a** and **3b**, which are reported herein.

Hucking, Kolc, and their associates studied the reactivity of 1-cyano-2-hydroxy-1,2-dihydroquinoline (**2c**) and reported its ring cleavage by the action of sodium hydroxide[4a] in dioxane or by photoirradiation.[4b] It is clear from the reaction mechanism in the above report[4a] that the analogue of **2c**, with 2-hydroxyl in a methyl ether form, *i.e.*, 1-cyano-2-methoxy-1,2-dihydroquinoline (**2a**), will not undergo ring cleavage by the action of sodium hydroxide. In fact, stirring of **2a** in dioxane with sodium hydroxide solution for a long time at room temperature resulted in entirely no reaction, proving the reported reaction mechanism.[4a] However, addition of 50% sodium hydroxide solution to the solution of **2a** or **2c** in methanol resulted in instant reaction and **1a** was formed. The same reaction was carried out on 2-cyano-1-methoxy-1,2-dihydroisoquinoline (**2b**) and 2-cyano-1-hydroxy-1,2-dihydroisoquinoline[5] (**2d**), and the reaction progressed instantly to form **1b** from both **2b** and **2d** (*cf.* Chart 2). It was then found that the reaction of **2a** or **2d** with the base progressed instantly and, since there was entirely no formation of the ring cleaved products, it was hard to believe that this reaction passed through the process[4a] of ring opening of **2a** or **2d**. By considering that this reaction progressed with direct attack of the base (OH^-) on the N-cyano group in methanol, followed by liberation of ^-OMe or ^-OH, as shown in Chart 2, the resulting product formation can be explained well.

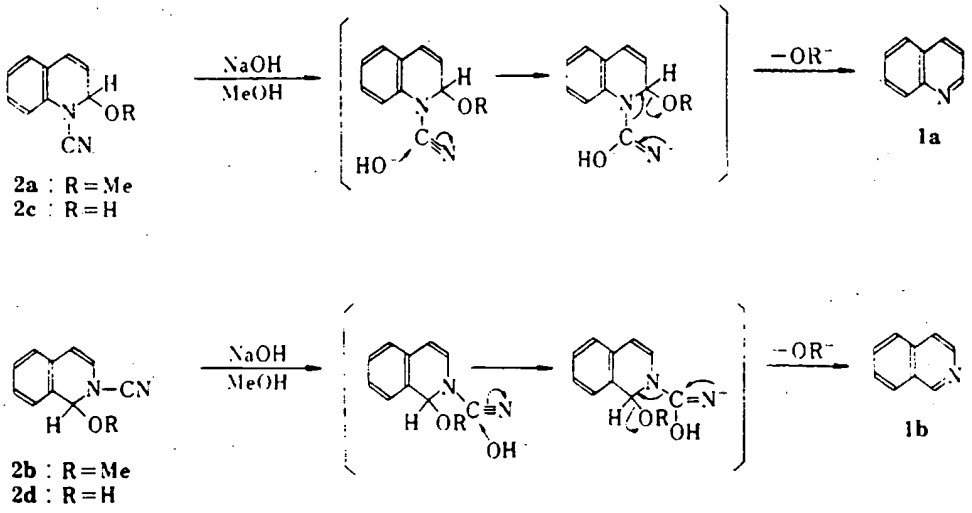


Chart 2

We reported previously[3] that methoxylation of 2-position in **2c** was catalyzed by a small quantity of cyanogen bromide in methanol at room temperature to form **2a**. The same application of a small amount of cyanogen bromide to **2d** in methanol resulted in quantitative formation of **2b**. Thus, the reactivity of 2-position in **2a** and **2c**, and that of 1-position in

3) Y. Hamada and M. Sugiura, *Yakugaku Zasshi*, **98**, 1 (1978); *idem*, *ibid.*, **98**, 1081 (1978).
4) *a*) B.J. Huckings and M.D. Johonson, *J. Chem. Soc. B*, **1966**, 63; *b*) J. Kolc and R.S. Becker, *J. Chem. Soc. Perkin Trans. II*, **1972**, 17; *idem*, *J. Phys. Chem.*, **72**, 997 (1968); *idem*, *ibid.*, **71**, 4045 (1967); *idem*, *J. Am. Chem. Soc.*, **91**, 6513 (1969).
5) T. Shimidzu, *Yakugaku Zasshi*, **1926** (No. 537), 943.

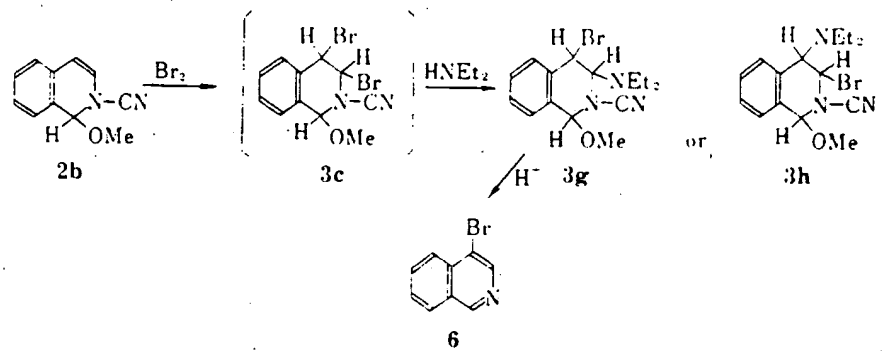


Chart 5

from **2b** and differs from that in the formation of **3d** from **2b**. The reason for this difference is now being examined (*cf.* Chart 5).

Next, an attempt was made to obtain 4-bromo-2-cyano-1-ethylthio-3-methoxy-1,2,3,4-tetrahydroisoquinoline (**3i**) from **2f**.

Compound (**2f**) was dissolved in methanol, bromine was added, and the reaction mixture was treated with saturated sodium carbonate solution, from which only **3b** was obtained (and not **3i**). In analogy with the conversion of oxygen to sulfur atoms in 1-position of **2b** described above, the oxygen atom in 1-position of **3b** might be exchanged with a sulfur atom, and comparative examination was made as described below. To a solution of **3b** in chloroform, bromine was added, and then ethanethiol was added dropwise, by which **3i** was obtained as expected. The structure of **3i** was confirmed from various spectral data and by the formation of **5** and **6** by hydrolysis with potassium cyanide or concentrated hydrochloric acid.

Similarly, the compound (**2e**) was treated with bromine in methanol and subsequently with saturated sodium carbonate solution. However, the product formed was **3a** and the

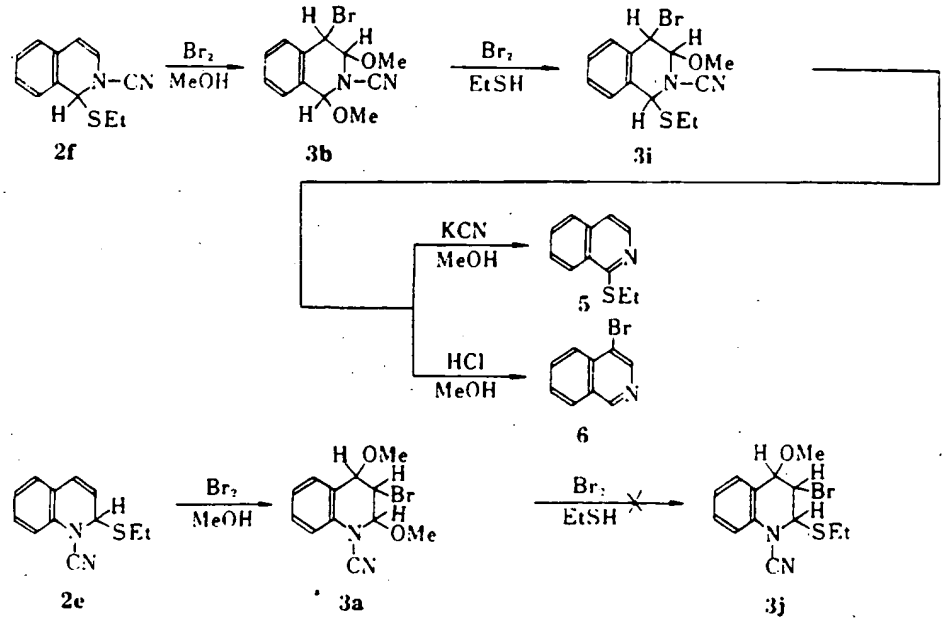


Chart 6

anticipated 3-bromo-1-cyano-2-ethylthio-4-methoxy-1,2,3,4-tetrahydroisoquinoline (**3j**) was not formed at all. Conversion of **3a** to **3j**, under the reaction conditions for the formation of **3i** from **3b**, was tried but the reaction did not progress at all. These facts indicated that there is a difference in reactivity between structure of tetrahydroquinoline and tetrahydroisoquinoline.

As shown above, reactivity of 2-cyano-tetrahydroisoquinoline derivatives (**3b,d,g,i**) differs according to the presence of sulfur atom bonded to the substituent and that of an oxygen atom. Alkaline hydrolysis of compounds (**3d,i**) bearing a sulfur atom in 1-position gives **5**, in which the sulfur atom in 1-position remains, while that of a compound (**3b**) bearing oxygen atom in 1-position gives **6**, in which the substituent in 4-position remains.[1] In acid hydrolysis, an interesting result was obtained that all of these compounds (**3b,d,g,i**) form **4** and **6**, in which the substituent in 4-position remains. It was learned from the result of these reaction that it would be necessary to pay special attention to the substituent in 1-position for the synthesis of isoquinoline derivatives having a substituent, using the intermediate obtained by the von Braun reaction.

We have already reported the formation of 4-chloroisoquinoline (**7**) by the hydrolysis of **3b** with concentrated hydrochloric acid in methanol,[1] when the hydrogen atoms in 3,4 position of **3b** are *trans*-oriented. However, the use of 50% acetic acid instead of hydrochloric acid as a catalyst gave easily 4-bromo-2-cyano-1-hydroxy-3-methoxy-1,2,3,4-tetrahydroisoquinoline

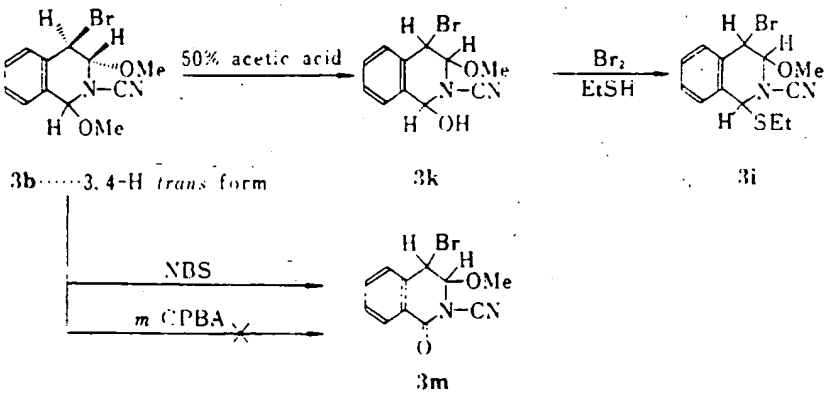


Chart 7

(**3k**), not aromatized, from **3b** and its structure was confirmed from various spectral data. Formation of **3k**, not aromatized, was considered to be due to the acidity of acetic acid used as a catalyst in this hydrolysis. Furthermore, reaction of **3k** with ethanethiol and bromine in chloroform resulted in the formation of **3i**, whose structure was confirmed from its IR spectrum. For the sake of comparison with 1-cyano-tetrahydroquinoline system, **3a** was treated in 50% acetic acid but the expected 3-bromo-1-cyano-2-hydroxy-4-methoxy-1,2,3,4-tetrahydroquinoline was not formed at all. Thus, the reaction with 50% acetic acid also differs according to the tetrahydroquinoline and tetrahydroisoquinoline skeleton.

Since the oxidation of **2a** and **2b** with *m*-CPBA respectively afforded **2g** and **2h**, the same oxidation of **3a** and **3b** was carried out. As shown in Chart 7, reaction of **3b** with *m*-CPBA in benzene did not produce 4-bromo-2-cyano-3-methoxy-1,2,3,4-tetrahydroisoquinolin-1-one (**3m**), while **3m** was obtained in 65% yield when **3b** was treated with N-bromosuccinimide (NBS).[6] Formation of **3m** was attempted by treatment of **2h** with bromine and sodium

6) R. Filler, *Chem. Rev.*, **63**, 21 (1963).

2b and **2d** became clear and in order to compare with the case of alcohol the reaction of **2a**,**b** with thiol was carried out.

Compound (**2a** or **2b**) was dissolved in chloroform, bromine and ethanethiol were added, and 1-cyano-2-ethylthio-1 2-dihydroquinoline (**2e**) was formed from **2a** and 2-cyano-1-ethylthio-1,2-dihydroisoquinoline (**2f**) from **2b**. This reaction is a conversion of oxygen to sulfur atoms. Oxidation of **2a** and **2b** with *m*-chloroperoxybenzoic acid (*m*-CPBA) resulted in the oxidation of the active position, as expected, and 1-cyano-1,2-dihydroquinolin-2-one (**2g**) was formed from **2a** and 2-cyano-1,2-dihydroisoquinolin-1-one (**2h**) from **2b**. The structures of **2g** and **2h** were confirmed by their hydrolysis, producing 1,2-dihydroquinolin-2-one (**2i**) and 1,2-dihydroisoquinolin-1-one (**2j**), respectively. The carbonyl group in 1-position of **2g** and 2-position of **2h** shows a strong absorption at 1700 and 1720 cm^{-1}, respectively, in their infrared (IR) spectra. It was therefore considered that they would form a hydrazone, and hydrazine hydrate was applied to **2g** and **2h**, by which a hydrazone (**2k**) was formed easily from **2h** but a hydrazone not from **2g**, which instead formed a hydrolyzed **2i** (*cf.* Chart 3).

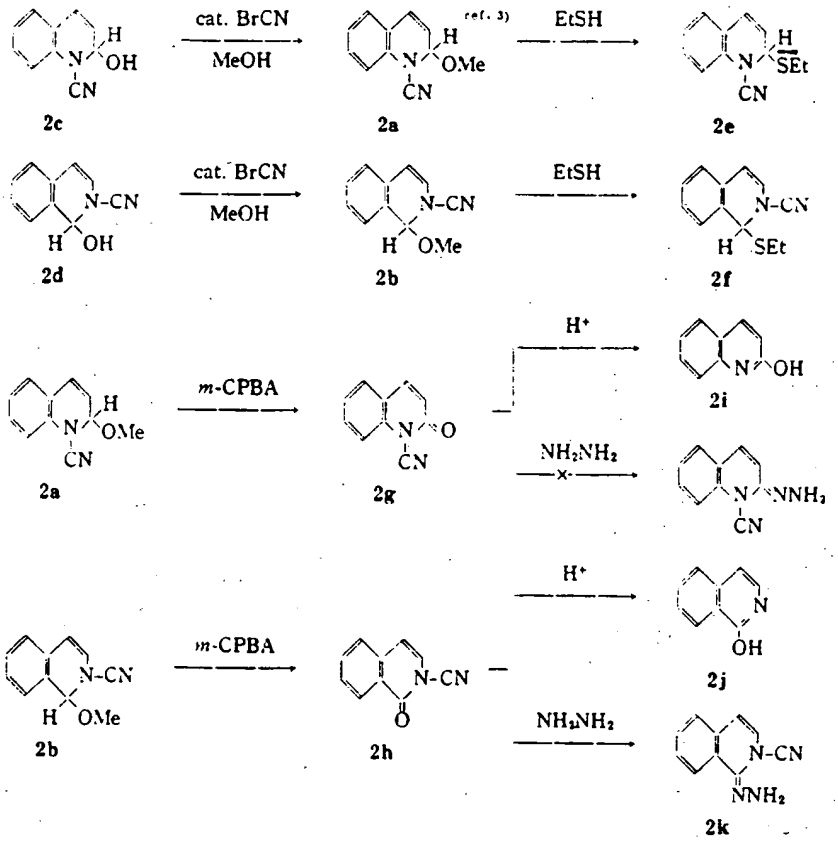


Chart 3

We showed in our previous paper[1] that the formation of 4-bromo-2-cyano-1,3-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**3b**) from **2b** was preceded by the intermediate formation of 2-cyano-3,4-dibromo-1-methoxy-1,2,3,4-tetrahydroisoquinoline (**3c**) (*cf.* Chart 4). Comparative examination were made on **3c** with alcohol and thiol. In the present series of work, **2b** was dissolved in chloroform, bromine was added, followed by ethanethiol, and then pyridine was added. This reaction resulted in the formation of a compound assumed from various spectral data to be 3-bromo-2-cyano-1,4-diethylthio-1,2,3,4-tetrahydroisoquinoline (**3d**) or 4-bromo-2-

cyano-1,3-diethylthio-1,2,3,4-tetrahydroisoquinoline (**3e**). It seemed impossible to determine the structure of this compound, whether **3d** or **3e**, from its spectral data and, therefore, the following reaction was carried out. This compound was dissolved in methanol and hydrolyzed with concentrated hydrochloric acid or potassium cyanide, resulting in the formation of 4-ethylthioisoquinoline (**4**) or 1-ethylthioisoquinoline (**5**). This fact denied the structure of **3e**, and the product was determined to be **3d**. The formation of **3d** from **2b** can be explained by considering that the reaction passes through formation of **3c**, which is converted to 2-cyano-3,4-dibromo-1-ethylthio-1,2,3,4-tetrahydroisoquinoline (**3f**) by the action of ethanethiol, and replacement of the bromo group in 4-position (benzylic) with ethanethiol in the presence of the base, finally resulting in the formation of **3d**. (*cf.* Chart 4). The present reaction was found to be different from that in the case[1] of **3b**.

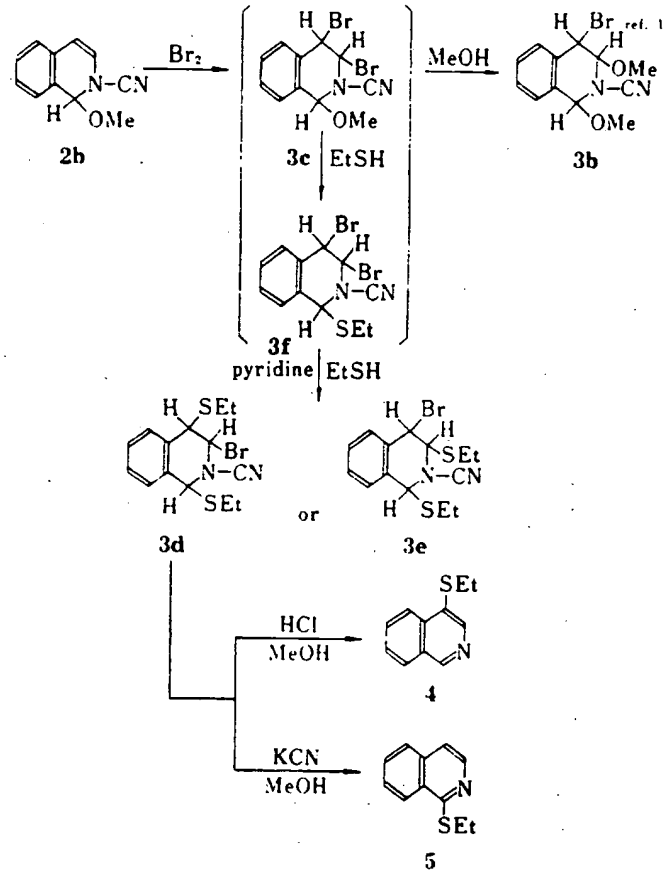


Chart 4

A similar reaction of **2b** with bromine in chloroform, followed by treatment with diethylamine gave a compound assumed from various spectral data to be 4-bromo-2-cyano-3-diethylamino-1-methoxy-1,2,3,4-tetrahydroisoquinoline (**3g**) or 3-bromo-2-cyano-4-diethylamino-1-methoxy-1,2,3,4-tetrahydroisoquinoline (**3h**). Since the compound formed 4-bromoisoquinoline (**6**) by acid hydrolysis, it was determined as **3g** and not **3h**. Formation of **3g** from **2b** passes through the intermediate formation of **3c** followed by the reaction of bromo group in its 3-position with diethylamine. The mechanism of this reaction is similar to that[1] of **3b**

carbonate in methanol[1,3] but the reaction resulted in quantitative recovery of **2h**. Treatment of **3a** with NBS also failed to give the anticipated 3-bromo-1-cyano-4-methoxy-1,2,3,4-tetrahydroquinolin-2-one. This reaction also seems to differ by the reactivity of tetrahydroquinoline and tetrahydroisoquinoline skeleton.

We have already reported the addition of alcohol or water to the N-cyano group in tetrahydroquinolines[3] and this addition reaction was also attempted with tetrahydroisoquinolines. As shown in Chart 8, a mixture of **3b** and 20% sodium hydroxide solution in the appropriate

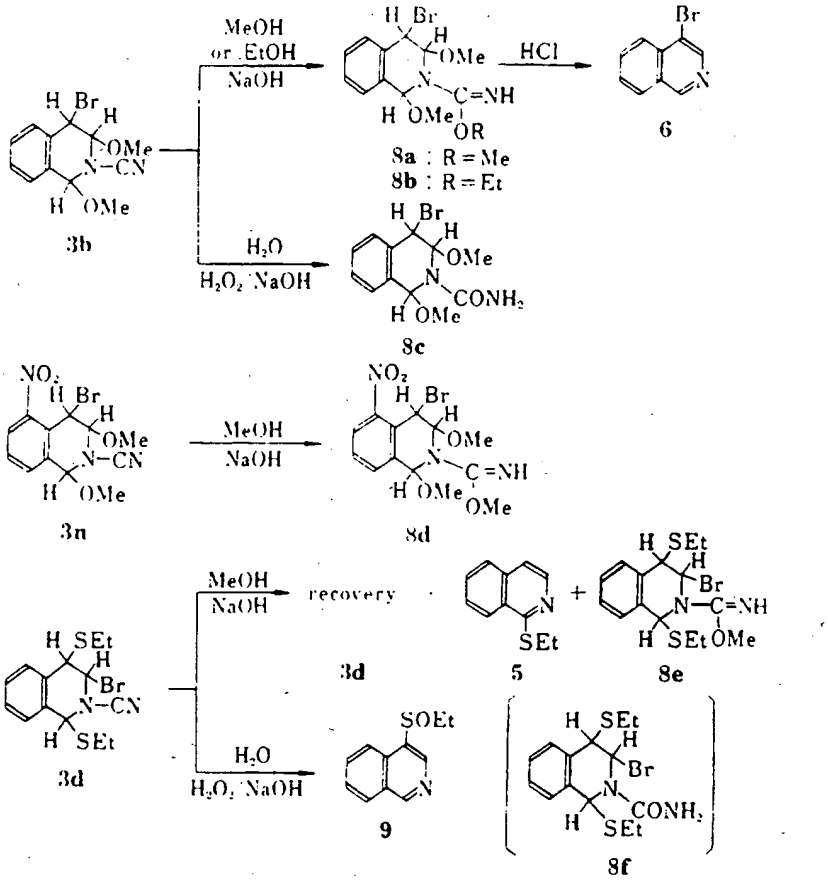


Chart 8

alcohol was refluxed for 1 hr to give imino ether compounds (**8a,b**). Hydrolysis of **8a** and **8b** with concentrated hydrochloric acid gave **6**. Compound **3b** also formed the corresponding carboxamide compound (**8c**) by the addition of water to N-cyano group in the presence of hydrogen peroxide in acetone. 4-Bromo-2-cyano-1,3-dimethoxy-5-nitro-1,2,3,4-tetrahydroisoquinoline[1] (**3n**) also underwent addition of methanol to N-cyano group to form an imino ether compound (**8d**). The imino ether compound (**8e**) was obtained only in a small amount from **3d** having a sulfur atom, the starting **3d** was recovered, and the product included **5**, which was formed by further progress of decomposition. Water addition reaction of **3d** failed to afford the expected carboxamide compound (**8f**), in spite of the anticipated facile progress of this reaction, and 4-ethylsulfinylisoquinoline (**9**) was obtained as a result of oxidation of the sulfur atom with attended aromatization.

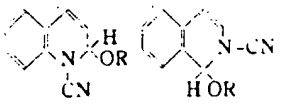
These experimental results indicated that there is hardly difference in the chemical reactivity of 1(or 2)-cyano-1,2-dihydroquinoline (**2a**) and -1,2-dihydroisoquinoline (**2b**) but there is a distinct difference in that between structure of the quinoline (**3a**) and isoquinoline (**3b**). This fact shows the importance of selecting one of these compounds for use as an intermediate in the syntheses of isoquinoline derivatives due to difference in the reactivity of nitrogen, oxygen or sulfur atoms present as a substituent in 1-,3- or 4-position of 1,2,3,4-tetrahydroisoquinolines.

Experimental

Gas chromatography was carried out with JGC Model 20-KFP, with FID detector (Japan Electronics, Tokyo), with a stainless steel column of 3 mm×1 m, liquid phase of 10% silicone SE-30, 30% PEG 20 M, 10% silicone OV-17, and 10% silicone XE-60; stationary phase of Chromosorb W-AW-DMCS, 60—80 mesh, carrier gas of N_2 at 50 ml/min. Nuclear magnetic resonance (NMR) spectra were taken with JEOL Model PS-100 (Japan Electronics, Tokyo), using tetramethylsilane (TMS) as internal standard. Mass spectra were taken with Hitachi Model M-52, and IR spectra with JASCO Model IRA-I (Japan Optics).

Reaction of 1-Cyano-2-methoxy(or hydroxy)-1,2-dihydroquinoline (2a, c) and 2-Cyano-1-methoxy (or hydroxy)-1,2-dihydroisoquinoline (2b, d) with Sodium Hydroxide——To a solution of 0.01 mol of **2a**, **2b**, **2c**, or **2d** in 30 ml of dioxane or methanol, 30 ml of 50% NaOH solution was added the mixture was stirred at room temperature for 5 min or 24 hr. This was poured into water, the solution was extracted with CH_2Cl_2 and the organic layer was evaporated after drying over anhyd. $MgSO_4$. The residue was identified with **2a** from IR spectra or with a commercial product. Yield of the products is listed in Table I.

Table I. Yield of Products from Reaction with Sodium Hydroxide

Starting material		Reaction conditions		Product	
Compounds No.	R	Time (min)	Solvent	Compounds No.	Yield (%)
 **2a, c**	**2b, d**				
2a	Me	24 hr	Dioxane	**2a** (Recovery)	93.5
2a	Me	5	Methanol	**1a**	99.9
2b	Me	5	Methanol	**1b**	99.5
2c	H	5	Methanol	**1a**	99.5
2d	H	5	Methanol	**1b**	99.7

2-Cyano-1-methoxy-1,2-dihydroisoquinoline (2b)——To a solution of 0.1 mol of **2d** in 100 ml of methanol, 0.01 mol of cyanogen bromide was added and the mixture was stirred at room temperature for 24 hr. Evaporation of methanol afforded **2b** as a residue and its yield and physical properties are listed in Table II.

Conversion of Oxygen Atom to Sulfur Atom——(i) To a solution of 0.05 mol of **2a**, **2b**, or **3a**, **b**, **k** and 0.1 mol of ethanethiol in 100 ml of $CHCl_3$, 20 ml of $CHCl_3$ solution prepared from 0.065 mol of Br_2 was added dropwise, with stirring at 0—5°, and the mixture was stirred at room temperature for 3 hr. This was poured into water, $CHCl_3$ layer was separated, and the solvent was evaporated after drying over anhyd. $MgSO_4$. Yield and physical properties of the products, **2e**, **2f**, or **3a**, **i**, are listed in Table II.

(ii) To a solution of 0.05 mol of **2b** in 100 ml of $CHCl_3$, 20 ml of $CHCl_3$ solution prepared from 0.065 mol of Br_2 was added dropwise under stirring at 0—5° for 0.5 hr, then 0.1 mol of ethanethiol was added, and the mixture was stirred at room temperature for 0.5 hr. To this mixture, 20 ml of pyridine was added at room temperature and the whole was stirred for 15 hr. This was processed as in (i) and the product was submitted to column chlomatography over SiO_2. Compound was obtained from the fraction eluted with benzene-$CHCl_3$ (1:1). Yield and physical properties of **3d** are given in Table II.

Oxidation with *m*-Chloroperoxybenzoic Acid (*m*-CPBA)——To a solution of 0.01 mol of **2a**, **2b**, or **3b** in 50 ml of $CHCl_3$, 0.025 mol of *m*-CPBA was added at 0—5° and the mixture was stirred at room temperature for 2 hr. To this mixture, 10% Na_2CO_3 solution was added to render the aqueous layer alkaline and $CHCl_3$

TABLE II. Yield and Physical Properties from Reaction with Methanol, Ethanethiol, or Diethylamine

Starting material Compounds No.	Reagent	Product Compounds No.	Yield (%)	IR $\nu_{max}^{CHCl_3}$ cm^{-1} C=C	-O-	N-CN	NMR (10% solution in $CDCl_3$) δ[a] 1-H	2-H	3-H	4-H	Formula	Analysis (%) Calcd. (Found) C	H	N
2d	Methanol	**2b**	99.0	1640	1045	2220, 2240	5.88 (s)	—	6.32 (d, $J_{3,4}$=7 Hz)	5.92	$C_{11}H_{10}N_2O$	70.95 (71.14)	5.41 (5.55)	15.05 (14.98)
2a	Ethanethiol	**2e**	93.2	1640	—	2220, 2240	—	5.72 (d) ($J_{2,3}$=5 Hz,	5.74 (d-d) $J_{3,4}$=10 Hz)	6.52 (d)	$C_{13}H_{12}N_2S$	66.63 (66.86	5.59 5.65	12.95 12.79)
2b	Ethanethiol	**2f**	95.4	1635	—	2220, 2240	6.20 (s)	—	6.27 (d, $J_{3,4}$=7 Hz)	5.96	$C_{13}H_{12}N_2S$	66.63 (66.79	5.59 5.36	12.95 12.21)
3a	Ethanethiol	**3a**[b] (Recovery)	98.8											
3b	Ethanethiol	**3i**	94.7	—	1065	2230, 2240	5.84 (s)	—	5.15 (d, $J_{3,4}$=2 Hz)	5.04	$C_{13}H_{15}BrN_2OS$	47.71 (47.98	4.62 4.57	8.56 8.75)
3k	Ethanethiol	**3i**[b]	92.6											
2b	Ethanethiol	**3d**	74.7	—	—	2220, 2240	5.84 (s)	—	5.12 (d, $J_{3,4}$=2 Hz)	5.04	$C_{14}H_{17}BrN_2S_2$	47.06 (46.86	4.80 5.09	7.84 7.97)
2b	Diethylamine	**3g**	63.0	—	1080	2230, 2240	5.64 (s)	—	5.04 (d, $J_{3,4}$=2 Hz)	5.00	$C_{18}H_{20}BrN_3O$	53.26 (53.44	5.96 6.08	12.42 12.54)

a) s: singlet; d: doublet; d-d: double doublets.
b) Identified with 3a or 3i from IR spectra.

TABLE III. Yield and Physical Properties of Oxidation Products

Starting material Compounds No.	Reagent	Products: Compounds No.	Yield (%)	mp (°C)	IR $\nu_{max}^{CHCl_3}$ cm^{-1}: N-CN	IR: C=O	NMR (10% solution in $CDCl_3$) δ: 3-H (Doublet)	NMR: 4-H (Doublet)	Formula	Analysis (%) Calcd. (Found): C	H	N
2a	MCPB[a]	**2g**	77.4	177—179	2240 2260	1700	6.62	7.80 (J=10 Hz)	$C_{10}H_6N_2O$	70.58 (70.44	3.55 3.29	16.46 16.62)
2b	MCPB[a]	**2h**	92.7	154—155	2250 2270	1710	7.00	6.56 (J=8 Hz)	$C_{10}H_6N_2O$	70.58 (70.39	3.55 3.46	16.46 16.53)
3b	MCPB[a]	**3b**[b] (Recovery)	98.8									
2g	Hydrazine[c]	**2i**[b]	87.5									
2h	Hydrazine[c]	**2k**	88.7	255—258 (Dec.)	2250 2270	—	7.76	7.00 (J=8 Hz)	$C_{10}H_8N_4$	65.20 (64.98	4.38 4.45	30.42 30.31)
3a	NBS	**3a**[b] (Recovery)	97.8									
3b	NBS	**3m** **3b**[b] (Recovery)	65.2 23.4	177—178	2240 2260	1720	5.34	5.18 (J=2 Hz)	$C_{11}H_8BrN_3O_2$	47.19 (46.87	3.22 3.01	9.93 9.75)

a) MCPB: *m*-chloroperoxybenzoic acid.
b) Identified with **2i** or **3b** from IR spectra.
c) Hydrazine: Hydrazine hydrate.

Table IV. Yield and Physical Properties of Hydrolysis Products

Starting material Compounds No.	Reagent	Products Compounds No.	Yield (%)	mp (°C) bp (°C/mmHg)	IR $\nu_{max}^{CHCl_3}$ cm^{-1} OH	IR $\nu_{max}^{CHCl_3}$ cm^{-1} C≡N	NMR[a] (10% solution in $CDCl_3$) δ 1-H	NMR[a] (10% solution in $CDCl_3$) δ 3-H	NMR[a] (10% solution in $CDCl_3$) δ 4-H	Formula	Analysis (%) Calcd. (Found) C	H	N
2g	HCl	**2i**[b]	83.4										
2h	HCl	**2j**	79.7	215—217	3440			8.40 (d, $J_{3,4}$ =8 Hz)	6.56	C_9H_7NO	74.47 (71.58	4.86 4.97	9.65 9.42)
3d	HCl	**4**	85.6	136—140 (3)			9.00 (s)	8.50 (s)		$C_{11}H_{11}NS$	69.80 (69.91	5.86 5.98	7.40 7.26)
3g	HCl	**6**[b]	76.3										
3i	HCl	**6**[b]	78.5										
8a	HCl	**6**[b]	86.1										
8b	HCl	**6**[b]	87.0										
3d	KCN	**5**	72.9	128—132 (1)				8.20 (d, $J_{3,4}$ =6 Hz)	7.18	$C_{11}H_{11}NS$	69.80 (69.77	5.86 6.03	7.40 7.54)
3i	KCN	**5**[b]	84.3										
3a	Acetic acid	**3a**[b] (Recovery)	98.7										
3b	Acetic acid	**3k**	86.1	134—135	3320	2220 2240	5.90 (s)	5.16 (d, $J_{3,4}$ =2 Hz)	5.04	$C_{11}H_{11}BrN_2O_2$	46.66 (46.57	3.92 4.11	9.89 10.07)

a) s: singlet; d: doublet.
b) Identified with **2i**, **8a**, **5**, or **6** from IR spectra.

TABLE V. Yield and Physical Properties of Products from Reaction with Methanol, Ethanol or Water

Starting material Compounds No.	Reaction conditions: Reagent	Temp. (°C)	Time (hr)	Products: Compounds No.	Yield (%)	IR $\nu_{max}^{CHCl_3}$ cm^{-1}: C=NH / C=O	-O- / S=O	NH / NH_2	NMR (10% solution in $CDCl_3$) δ[a]: 1-H (s)	3-H (d, J=2 Hz)	4-H	Formula	Analysis (%) Calcd. (Found): C	H	N
3b	Methanol	70	1	**8a**[b]	96.4	1630	1070	3370	6.18	5.82	5.18	$C_{12}H_{17}BrN_2O_3$	47.43 (47.49	5.21 5.50	8.51 8.39)
3b	Ethanol	70	1	**8b**	95.7	1630	1070	3370	6.18	5.84	5.18	$C_{11}H_{19}BrN_2O_3$	48.99 (49.14	5.58 5.76	8.16 8.05)
3d	Methanol	R.T.[f]	1	**3d**[c] (Recovery) 50.0											
				5[c] 20.0											
				8e 20.0	1625	1070	3380	6.32	5.88	5.24	$C_{16}H_{21}BrN_2OS_2$	46.27 (46.39	5.44 5.22	7.19 6.98)
3n	Methanol	R.T.[f]	3	**8d**	82.6	1635	1060	3360	6.20	5.84	5.18	$C_{13}H_{16}BrN_3O_5$	41.73 (42.04	4.31 4.55	11.23 11.30)
3b	Water	R.T.[f]	1	**8c**[d]	77.9	1680	1070	3400 3520	6.12	6.12	5.16	$C_{12}H_{15}BrN_2O_3$	45.73 (46.01	4.80 4.87	8.89 8.91)
3d	Water	R.T.[f]	1	**9**	68.5	—	1130	—	9.36	9.04[e]	—	$C_{11}H_{11}NOS$	64.36 (64.57	5.40 5.19	6.82 6.99)

a) s: singlet; d: doublet.
b) mp 88—90° (*n*-hexane).
c) Identified with **8d** or **5** from IR spectra.
d) mp 144—145° (benzene).
e) Singlet.
f) R.T.=room temperature.

layer was separated. $CHCl_3$ was evaporated after drying over anhyd. $MgSO_4$ and the residue was recrystallized from benzene–*n*-hexane (1 : 1) to **2g**, **2h**, or **3b**.

To a solution of 0.01 mol of **2g** or **2h** in 20 ml of methanol, 0.02 mol of hydrazine hydrate was added and the mixture was stirred at room temperature for 2 hr. Methanol was evaporated under a reduced pressure and **2i** or **2k** was obtained as crystals. Yield and physical properties of **2g**, **2h**, **2i**, **2k**, and **3b** are listed in Table III.

Hydrolysis——(i) A mixture of 30 ml of methanol solution of 0.01 mol of **2g**, **2h**, **3d**, **g**, **i**, or **8a**, **b** and 30 ml of concentrated HCl was refluxed for 3 hr, the reaction mixture was concentrated under a reduced pressure, 20 ml of water was added, and made alkaline with 20% NaOH solution. This mixture was extracted with CH_2Cl_2 and the organic solvent was evaporated after drying over anhyd. $MgSO_4$. The residual oil was purified by distillation to give **2i**, **2j**, **4**, or **6**.

(ii) To a solution of 0.01 mol **3d** or **3i** in 30 ml of methanol, 0.05 mol of KCN and 10 ml of water were added, the mixture was refluxed for 6 hr, and poured into water. This was extracted with CH_2Cl_2 and the solvent was evaporated after drying over anhyd. $MgSO_4$. Purification of the residual oil by distillation afforded **5**.

(iii) A mixture of 0.01 mol of **3a** or **3b** in 50% AcOH was heated at 65° for 12 hr, neutralized with $NaHCO_3$, and extracted with CH_2Cl_2. The organic solvent was evaporated after drying over anhyd. $MgSO_4$, and the residue was recrystallized from benzene–*n*-hexane (1 : 1) to **3a** or **3k**.

Yield and physical properties of **2i**, **2j**, **3a**, **3k**, and **4**—**6** are listed in Table IV.

4-Bromo-2-cyano-3-diethylamino-1-methoxy-1,2,3,4-tetrahydroisoquinoline (3g)——To a solution of 0.05 mol of **2b** in 100 ml of $CHCl_3$, 20 ml of $CHCl_3$ solution prepared from 0.07 mol of bromine was added dropwise with stirring at 0—5° during 0.5 hr, 20 ml of diethylamine was added, and the mixture was stirred for 24 hr. This was poured into water, chloroform layer was separated, and the solvent was evaporated after drying over anhyd. $MgSO_4$. The residue was chromatographed over SiO_2 and the fraction eluted with benzene–*n*-hexane (1 : 1) was separated and purified to **3g** with checking by gas chromatography. Yield and physical properties of **3g** are listed in Table II.

Bromination of 2e, 2f, and 2h——To a solution of 0.05 mol of **2e**, **2f**, or **2h** in 100 ml of methanol, 0.065 mol of Br_2 was added at 0—5°, saturated solution prepared from 0.6 equivalent of Na_2CO_3 was added, and the mixture was stirred at room temperature for 3 hr. This was poured into water, extracted with CH_2Cl_2, and the solvent was evaporated from the extract after drying over anhyd. $MgSO_4$. The residue was identified as **3a**,[3] **3b**,[3] or **2h** from their IR spectra. Their yield was 99.5, 99.5, and 99.8%, respectively.

Oxidation with N-Bromosuccinimide (NBS)——To a solution of 0.02 mol of **3a** or **3b** in 100 ml of CCl_4, 0.05 mol of NBS was added and the mixture was refluxed for 24 hr. The crystals that separated out were filtered off, the filtrate was concentrated, and the residual substance was chromatographed over SiO_2. From the fraction eluted with benzene, **3a** or **3m** was separated with checking by gas chromatography. Yield and physical properties of **3a** and **3m** are given in Table III.

Addition of Alcohol to N-Cyano Group——To a solution of 0.01 mol of **3b**, **3d**, or **3n** in 30 ml of methanol or ethanol, 4 ml of 20% NaOH solution was added and the mixture was stirred for 1 hr at 70° or room temperature. This mixture was poured into water, extracted with dichloromethane, and the solvent was evaporated from the extract after drying over anhyd. $MgSO_4$. The residue afforded **8a**, **b**, **8d**, **e**, **3d**, or **5**. Yield and physical properties of these products are listed in Table V.

Addition of Water to N-Cyano Group——To a mixture of 0.01 mol of **3b** or **3d** in 30 ml of acetone and 1 ml of 10% NaOH solution, 15 ml of 10% H_2O_2 was added dropwise at 0—5°, the whole was stirred at room temperature for 1 hr, and poured into water. This mixture was extracted with CH_2Cl_2 and the solvent was evaporated from the extract after drying over anhyd. $MgSO_4$. The residue was chromatographed over Al_2O_3 column, the fraction eluted with benzene was discarded, and that eluted with methanol–CH_2Cl_2 (1 : 9) afforded **8c** or **9**. Yield and physical properties of these products are given in Table V.

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